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Pattern of Malformations in the Axial Skeleton in Human Trisomy 18 Fetuses

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We examined and described the development and abnormalities of the axial skeleton in 10 human trisomy 18 fetuses. Whole-body radiographs and radiographs of midsagittal tissue blocks of the cranial base and the spine were studied. In 3 fetuses no spinal radiographs were available. Seven osseous regions or fields along the body axis were analyzed, four in the spine, and three in the cranial base and nasal bones. Malformations occurred in the occipital field in all fetuses. This was a characteristic notching, either unilateral or bilateral, of the basilar part of the occipital bone. Nasal bones were abnormal in 8 cases, either absent or hypoplastic. Malformations were found in the thoracic and/or lumbosacral field in 7 fetuses. A single abnormality was found in the cervical spine in one fetus. The pattern of axial skeletal malformation in trisomy 18 fetuses recorded in the present study has not been described previously. Axial skeletal radiography should be included in autopsies of fetuses when chromosome disorders are present or suspected. The methods applied here are unaffected by autolysis.

KEY WORDS: development, skeleton, fetal, genetic, radiography, trisomy 18

INTRODUCTION

A previous investigation of the axial skeleton in human anencephalic fetuses showed that malformations occurring in the axial skeleton could be related to the course of the notochord, which initiates the closure of the neural tube and the development of the axial skeleton [Kjær et al., 1994a]. This study showed regional differences in the occurrence of malformations along the axial skeleton, which were related to the various sites of rachischisis. These axial skeletal analyses proved to be important in distinguishing between malformation (anencephaly) and disruption (amniotic band sequence with brain involvement) [Keeling and Kjær, 1994].

In light of these findings, we thought it relevant to investigate the pattern of malformations in the axial skeleton in fetuses with genetic disorders. Such investigations have not been undertaken previously, and the present study is the first in a series of investigations mapping the axial skeleton in genetic anomalies.

The purpose of the present investigation was to analyze the axial skeleton in fetuses with trisomy 18, and to define the fields in the axial skeleton affected in this chromosomal disorder.

MATERIALS AND METHODS

Materials

Ten human fetuses (4 males, 6 females) with trisomy 18 were included in the study. None had a defect of neural tube closure.

The fetuses were between 15–20 weeks of gestational age (GA). They were examined with parental consent at the Royal Hospital for Sick Children, Edinburgh, Scotland, and at the Hvidovre University Hospital, Hvidovre, Denmark.

Methods

Whole-body radiographs in frontal and lateral projections were taken, followed by dissection and further radiological analysis. A midsagittal tissue block of the cranial base and the entire spine were isolated by two sagittal incisions at the lateral border of the foramen magnum, continuing along the lateral aspects of the entire spine [Kjær, 1990a,b; Kjær et al., 1994a,b]. The interposed midsagittal segment was radiographed in frontal and lateral projections. In three cases the cranial base was separated from the spine and radiographed before sectioning. In 3 of the female fetuses no radiographs of the spine were available. Radiographs of fetal hands and feet were used for skeletal maturity assessment [Kjær, 1974]. Using this standard measure-

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ment, standards for normal axial skeletal development were calculated and used as a basis for comparison in individual cases [Kjær, 1990a; Kjær et al., 1993; Kyrkanides et al., 1993; Sandickioglu et al., 1994]. A Grenz Ray radiographic apparatus (Hewlett Packard Faxitron Model 43855A, McMinnville, OR, USA) was used with Kodak X-Omat MA film. The tissue was placed directly on the film envelope. Depending on the size of the specimen, the tube voltage varied between 20–60 kV, and the exposure time between 10–60 sec at 2.8–3.0 mA.

The following seven osseous regions or fields of the axial skeleton, illustrated in Figures 1 and 2, were analyzed separately: the sacral, lumbar, thoracic, and cervical vertebral segments of the spine, the basilar part of the occipital bone, the postsphenoid component of the sphenoid bone, and the nasal bones.

RESULTS

Cranial Base

Malformations were seen in the basilar part of the occipital bone in all fetuses. In one fetus this bone was short and triangular. In 6 fetuses unilateral notching was present, and in 3, bilateral notching was recorded (Fig. 3). In all cases, the notching was located in the same anteroposterior situation, at the junction of the anterior third and middle third of the lateral borders of the bone. Additionally, the postsphenoid component of the sphenoid bone (except in one fetus) had bilateral ossification centers, which in the larger fetuses were fused along the body axis (Fig. 3).

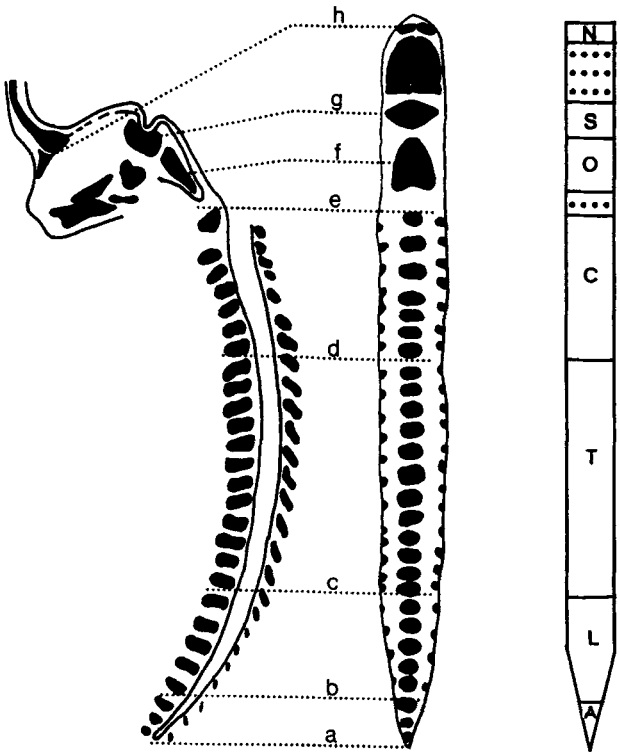

Fig. 1. Drawing of axial skeleton from a human fetus, 16 weeks of gestational age, in lateral view (left) and frontal view (center). Lines a–h indicate axial developmental fields, marked schematically in frontal view (right). The coccygeal field between lines a–b is indicated by A, the lumbar field between lines b–c by L, the thoracic field between lines c–d by T, and the cervical field between lines d–e by C. The basilar part of the occipital bone, indicated by f, is marked O, the postsphenoid bone, indicated by g, is marked S, and the nasal bones, indicated by h, are marked N.

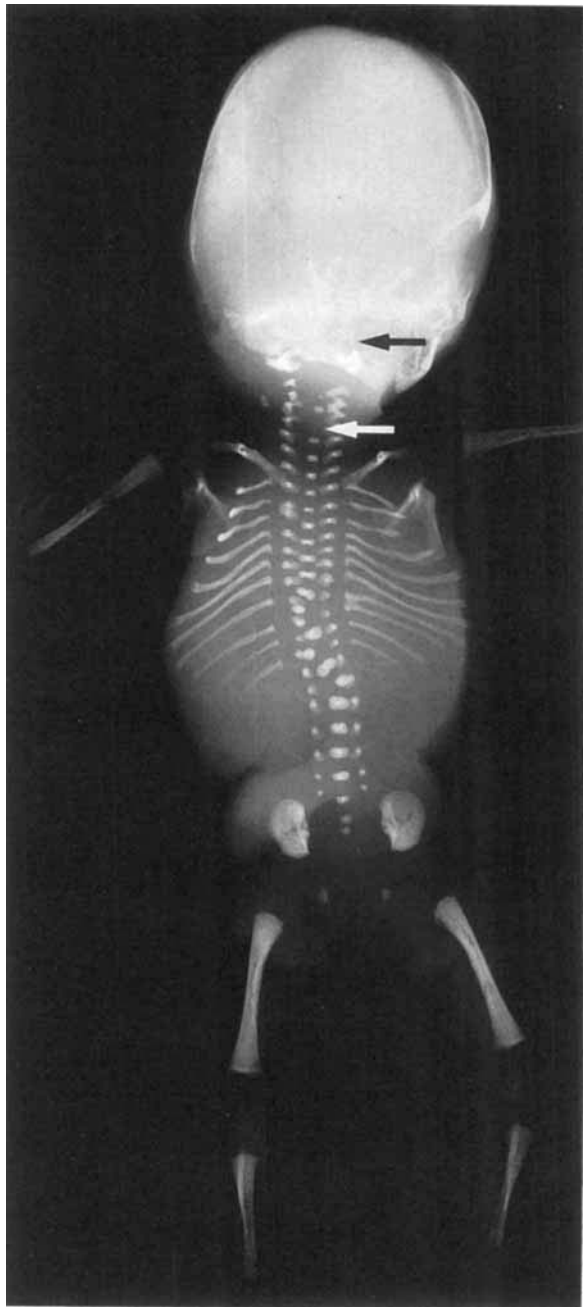

Fig. 2. Whole-body radiograph of human fetus with trisomy 18 in frontal view, 18 weeks of gestational age. Note malformed vertebral bodies in thoracic and lumbar regions of the spine. In the cervical spine there is agenesis of a vertebral body (white arrow). The malformed basilar part of the occipital bone (black arrow) is hardly visible in the whole-body radiograph (×0.8).

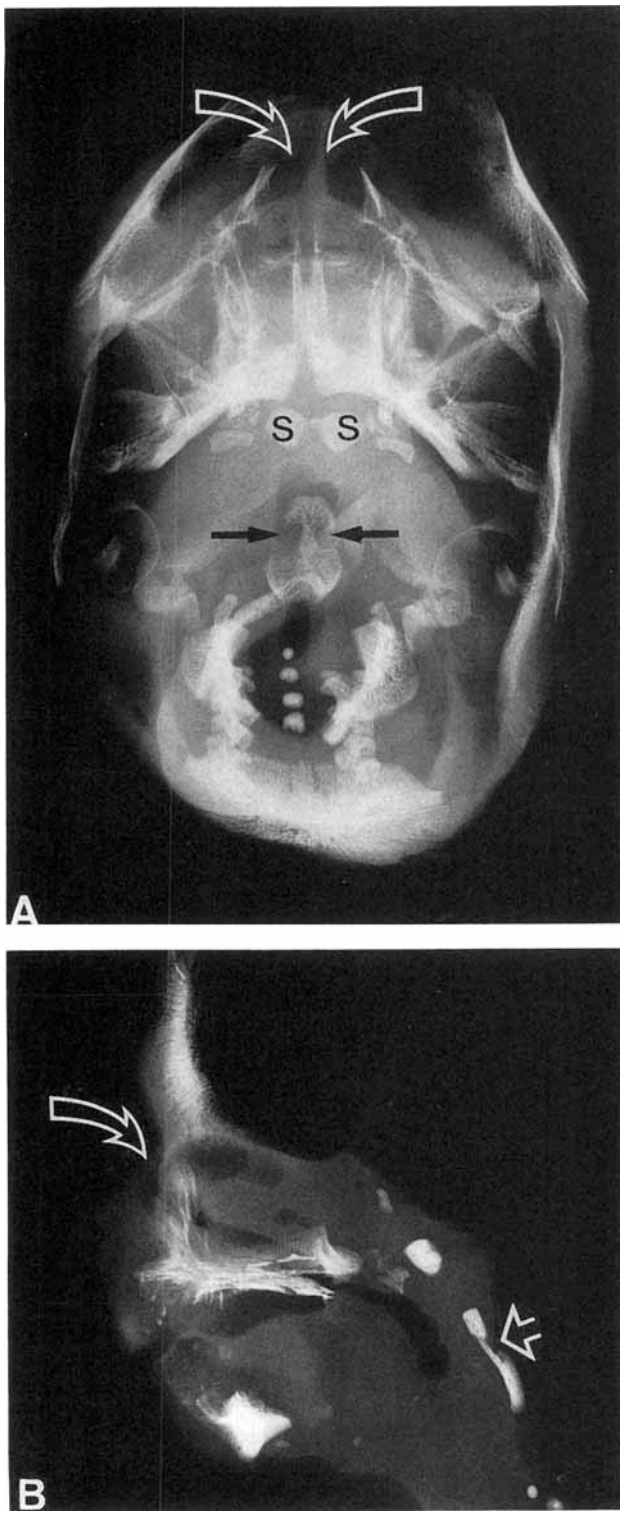

Fig. 3. Radiographs of cranial base, including mandible from a human fetus with trisomy 18, 19 weeks of gestational age. **A:** Horizontal view. Note bilateral notching of basilar part of occipital bone (black arrows), the bilateral ossification centers (s) of postsphenoid bone component, and agenesis of nasal bones in the field indicated (white arrows) (×2). **B:** Lateral view of midsagittal segment of cranial base, constituting part of the upper axial skeleton. Note malformation of the basilar part of the occipital bone (straight arrow), and agenesis of nasal bones in the field indicated (curved arrow) (×2).

Nasal Bones

The nasal bones were normal in two cases. Short nasal bones occurred in 3 cases and in 5 cases the nasal bones were absent (Figs. 3–5).

Spine

In all fetuses where the vertebral column was radiographed, malformations were seen in the thoracic and/or lumbosacral fields (Figs. 2, 4, and 5). The types of malformation registered were partial clefting of vertebral bodies in lateral radiographic projection, and dislocation of vertebral bodies in frontal radiographic projection. The only abnormality in the cervical region was agenesis of a single vertebral body (Fig. 2).

DISCUSSION

Since the first report by Edwards et al. [1960], trisomy 18 syndrome has been the subject of many careful studies, mostly concerned with phenotypic and visceral malformations and malformations in the muscular system [Barash et al., 1970; Bersu and Ramirez-Castro, 1977; Ramirez-Castro and Bersu, 1978; Gilbert and Opitz, 1982; Moerman et al., 1982; Kinoshita et al., 1989; Keeling and Boyd, 1993; Keeling, 1994]. Similar

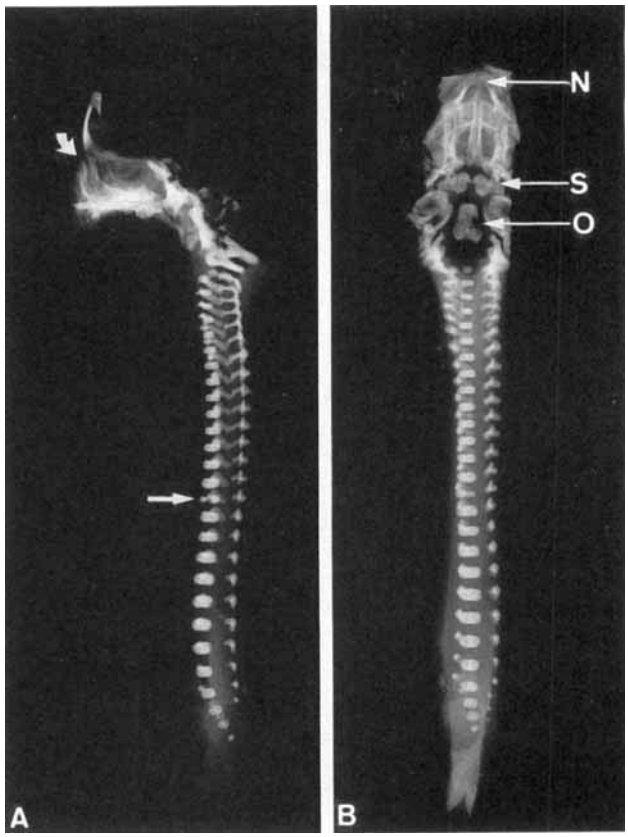

Fig. 4. Radiographs of axial skeleton of human fetus with trisomy 18, 18 weeks of gestational age. **A:** Lateral view. Note agenesis of nasal bones in the field indicated (curved arrow), and malformation of eighth thoracic vertebral body (straight arrow). **B:** Frontal view. Note agenesis of nasal bones in developmental field N, bilateral ossification centers of the postsphenoid bone located in field S, and unilateral notching of the basilar part of the occipital bone (O) (×0.9).

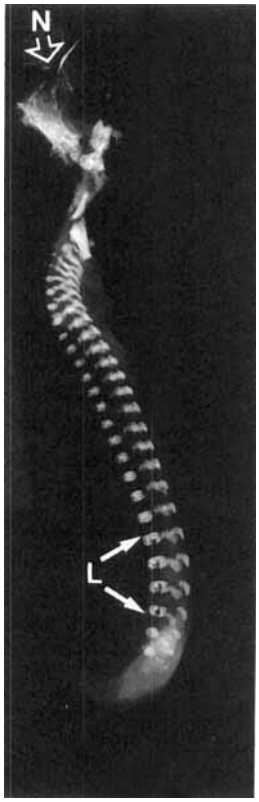

Fig. 5. Radiograph of axial skeleton of human fetus with trisomy 18, 20 weeks of gestational age. Lateral view. Note cleft of four vertebral bodies located in lumbar field (L). Slight contour of nasal bones is visible in the field marked N (×0.9).

studies are available on trisomy 13 and trisomy 21 [Colacino and Pettersen, 1978; Opitz et al., 1979].

Studies of skeletal development in trisomy 18 have concentrated on limb malformations [Benacerraf et al., 1986; Sepulveda et al., 1995], but cranial abnormalities accompanying cerebral malformations have also been reported [Nicolaides et al., 1992].

The pattern of axial skeletal malformations in trisomy 18 fetuses has not been described previously.

The most common and distinctive abnormality in the axial skeleton in trisomy 18 fetuses is seen in the basilar part of the occipital bone. The malformations seen are similar and they always occur in the same region of the bone. The morphology of the malformation, characterized by deep notching, is quite different from that seen previously [Kjær et al., 1994a; Kjær and Fischer Hansen, 1995], and such abnormalities are never seen in normal fetuses [Kyrkanides et al., 1993]. A previous study demonstrated that bilateral ossification of the postsphenoid bone can be seen in about one half of aborted fetuses [Kjær, 1990b]. However, in all but one of the trisomy 18 fetuses, ossification of the sphenoid bone appeared bilateral. The significance of this morphological feature is not known. It may be related to differences in the timing of the development and ossification of the postsphenoid bone.

In the present material, reduced size or agenesis of the nasal bones was present. This pattern does not occur in normal development [Sandickioglu et al., 1994], and obviously explains the abnormal appearance of the upturned nose in this syndrome [Gilbert and Opitz, 1982]. Agenesis of the nasal bone has been described previously in patients with trisomy 21 [Frostad et al., 1971], among whom 8% in a group of 121 individuals had nasal bone agenesis.

The type of spinal malformations recorded resembles those seen in anencephaly and rachischisis without neck involvement [Kjær et al., 1994a]. The only abnormalities in the cervical region were hypoplasia of a single vertebral body, unlike that seen in anencephaly, and rachischisis with neck involvement, where double bodies were seen in frontal projection [Kjær et al., 1994a].

Previous studies have shown that the prenatal axial skeleton is a useful marker of pathological development of the central nervous system [Kjær, 1994]. The present study demonstrates that the axial skeleton of trisomy 18 fetuses with normal neural tube closure exhibits specific phenotypic abnormalities which undoubtedly are related to the genotype. These findings should be added to the inventory of abnormalities which has accumulated for this syndrome. The abnormalities described here are of practical as well as academic significance.

The value of skeletal investigations in autolysed material has already been demonstrated [Kjær and Fischer Hansen, 1995], and in cases where chromosome culture cannot be undertaken, analysis of the axial skeleton can probably confirm or refute a suspicion of trisomy 18. We stress, therefore, the importance of radiography of the axial skeleton in future investigations of dysmorphic or malformed fetuses.

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